Satoh *et al.*
Egyptian Journal of Forensic Sciences (2023) 13:33
https://doi.org/10.1186/s41935-023-00352-3

Egyptian Journal of Forensic Sciences

CASE REPORT Open Access

A fatal case of fulminant group: a streptococcal infection in a neonate

Fumiko Satoh[1*], Wataru Irie[1], Chizuko Sasaki[1], Eriko Ochiai[1] and Maho Kondo[1]

Abstract

Background Fulminant hemolytic streptococcal infection is a condition of sudden onset and rapidly progressing septic shock caused by *Streptococcus pyogenes*. It causes beta (complete) hemolysis. Although type A *Streptococcus* occurs more frequently, all streptococci that cause beta-hemolysis are eligible as causes. This report describes a rare autopsy case of fulminant group A streptococcal infection in a neonate.

Case presentation A 16-day-old girl, 3300 g, born by spontaneous delivery at 41 weeks 1 day, experienced a 1-day history of low-grade fever, malaise, and a few hours of cyanosis and anuria, prompting her parents to bring her to the hospital. Her eldest brother, who lived with her, had been infected with *Streptococcus* approximately one month earlier, and had been treated with ten days of antibiotics. The infant died three hours after presentation. Autopsy findings indicated her to be 52 cm in length, weighing 3585 g, with medium build and normal nutrition. Her lungs were slightly oligemic with decreased volumes. The liver and kidneys were mildly enlarged. The spleen was markedly enlarged. The adrenal glands showed diffuse cortical hemorrhage (Fig. 1). There was some thymic atrophy (thymus weight 7.4 g, < 1 SD below the mean). Histopathological findings included chronic and neutrophilic infiltration of the tonsils and multiple septic emboli containing cocci in the lungs. Perivascular inflammatory cell infiltrates were observed in the lungs, myocardium, kidneys, adrenal glands, brain, meninges, and liver, with micro-necrotic changes in the kidneys and liver. Fibrin thrombi were observed in multiple renal glomeruli. Hemophagocytosis by macrophages was observed in the spleen, liver, lymph nodes, bone marrow, and adrenal glands. Immunostaining showed positive results for group A *Streptococcus* antibody in the tonsils, with bacterial masses. Blood cultures were positive for group A *Streptococcus pyogenes*.

Conclusions Because of the lower respiratory tract infection and suspected sibling transmission, in addition to the adrenal hemorrhages, a diagnosis of fulminant sepsis with group A *Streptococcus pyogenes* with associated Waterhouse–Friderichsen syndrome was made.

Keywords Autopsy, Fulminant group A streptococcal infection, Hemophagocytosis, Immunohistochemistry, Neonate, Sepsis, Waterhouse–Friderichsen syndrome

Background

Streptococcus pyogenes, also known as group A streptococcus (GAS), can cause a broad range of infections and complications, from minor illnesses such as pharyngitis and impetigo (noninvasive disease) to very severe and deadly infections (invasive disease), such as necrotizing fasciitis and streptococcal toxic shock syndrome, and postinfectious sequelae such as rheumatic heart diseases (Martin et al. 2015). The epidemiology of fulminant group A streptococcal infection varies greatly among different populations. Incidence in the USA is approximately 11,000–13,000 per year, including cellulitis with sepsis, pneumonia, and necrotizing fasciitis. There are > 500,000 deaths per year worldwide

*Correspondence:
Fumiko Satoh
fumiko-s@med.kitasato-u.ac.jp
[1] Department of Legal Medicine, Kitasato University School of Medicine, 1-15-1, Kitasato, Minamiku, Sagamihara, Kanagawa 252-0374, Japan

(Carapetis et al. 2005). In Japan, fulminant group A streptococcal infection was first reported in 1992. Since then, 100–200 cases have been confirmed annually. In the paediatric population, annual incidence reportedly varies worldwide.from 2.5/100,000 to 101/100,000 (Hua et al. 2019). Although immunocompromised patients, children, and elderly people were originally thought to be at increased risk, it is now believed that healthy people of any age can be affected (Stevens 1992; Weiss and Laverdière 1997; Kato et al. 2018).

Here, we describe an autopsy case of a previously healthy neonate who died suddenly of fulminant group A streptococcal infection, possibly due to sibling transmission.

Case presentation

A 16-day-old girl with a birth weight of 3300 g, gestational history of 41 weeks and 1 day, and spontaneous delivery was examined. She had no medical history. She had lived with her parents and two older brothers, aged 5 years and 1 year. The older brother had been diagnosed with streptococcal pharyngitis approximately one month before her death; he had been treated with 10 days of antibiotics and recovered. On the evening of the day before her death, she started drinking less milk and showed a slight decrease in vitality. When she became cyanotic and stopped urinating, she was transported to a hospital emergency room, where she was found to be breathing with considerable effort, with a heart rate of 220 beats per minute, and general cyanosis. Her body temperature was 37.5 °C. Heart rate at the time of transport was 140 beats per minute, with weak blood pressure and peripheral coldness.

The patient was intubated and a central line was inserted. Cardiac agonists, sodium bicarbonate, and antibiotics were administered, but she became unresponsive and died approximately 3 h after admission. Because the cause of death was unknown, an autopsy was performed about 1.5 days after death.

External examination

Table 1 shows the normal ranges of measurements for neonatal girls. Body weight was normal at 3585 g. She was 52 cm in length, with medium build and normal nutrition. Prominent lividity was noted. External examination revealed no evidence of malformation or trauma.

Autopsy findings

The thymus was somewhat atrophic, weighing 7.4 g (< 1 S.D below the mean). Her heart weight was normal at 25.4 g, with bleeding in the epicardium and myocardium. Left and right ventricle walls were of normal thickness. There was a small amount of intracardiac blood. The foramen ovale was membranous and open. No malformation was found. There was no enlargement or redness of the tonsils. The tracheal mucosa was mildly erythematous, with a small amount of serosanguineous fluid. Lung weights were within normal limits, 38.2 g on the left and 42.9 g on the right. The lungs were slightly oligemic with poor air content. Liver weight was within normal limits, 235 g. The spleen was markedly enlarged, weighing 25.4 g. Both kidneys were enlarged, each weighing twice the normal average, 25.2 g left/24.9 g right, with pale renal pelvis. The adrenal gland weights were slightly increased, 4.1 g left/3.9 g right, with diffuse bilateral cortical hemorrhage (Fig. 1). A large parietal scalp hemorrhage was noted. The brain weight was normal at 401 g, with no swelling or hemorrhage.

Table 1 Comparison of height, weight, and organ weights with the mean for neonatal females

	Case	Newborn girl mean
Height (cm)	52	49.99 ± 4.08
Body weight (kg)	3.69	2.92 ± 0.92
Thymus (g)	7.4	14.02 ± 7.57
Heart (g)	25.4	20.36 ± 7.84
Lungs (left/right) (g)	38.2/42.9	29.15 ± 11.41/35.59 ± 15.40
Liver (g)	235	131.11 ± 41.93
Spleen (g)	25.4	9.78 ± 4.03
Kidneys (left/right) (g)	25.2/24.9	12.73 ± 4.63/12.95 ± 6.92
Adrenal glands (left/right) (g)	4.1/3.9	2.39 ± 0.95/2.26 ± 0.92
Brain (g)	401	411.1 ± 80.67

Questionnaire Research Performed by the Japanese Society of Legal Medicine (2015) Weights and sizes of internal organs measured in forensic autopsy cases from 2009 to 2013 in Japan. In: Japanese Society of Legal Medicine, Research report. Available via DIALOG

Histological findings

Hematoxylin–eosin (H&E) staining and sectioning was performed on all organs. The kidneys were also stained with Phosphotungstic Acid-Hematoxylin (PTAH) for fibrin and the lung tissue underwent Gram staining, Periodic acid-Schiff (PAS) staining, Grocott, and Ziehl–Neelsen staining. Immunostaining was performed on tonsil tissue using anti-group A *Streptococcus* antibody as the primary antibody.

Neutrophilic and chronic inflammation involved the tonsils. The lungs contained multiple coccal emboli in the blood vessels. Inflammatory cell infiltrates lacked neutrophilic infiltration in some coccal masses, with localised necrotic nodules in the lung (Fig. 2). As necrosis was observed in part of the lung, PAS and Grocott and Ziehl–Neelsen stains were performed on sections of the lung to rule out fungal infections, Mycobacterium tuberculosis and other anti-acid infections,

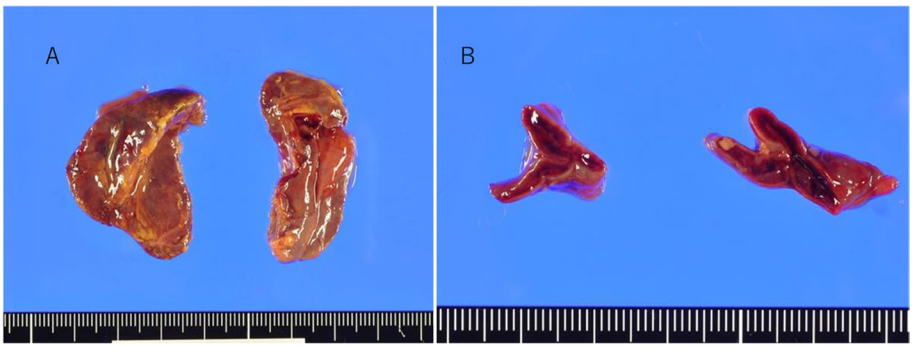

Fig. 1 Bilateral adrenal hemorrhages. **A** Right and left adrenal macroscopic images. **B** Left and right transverse section surface images

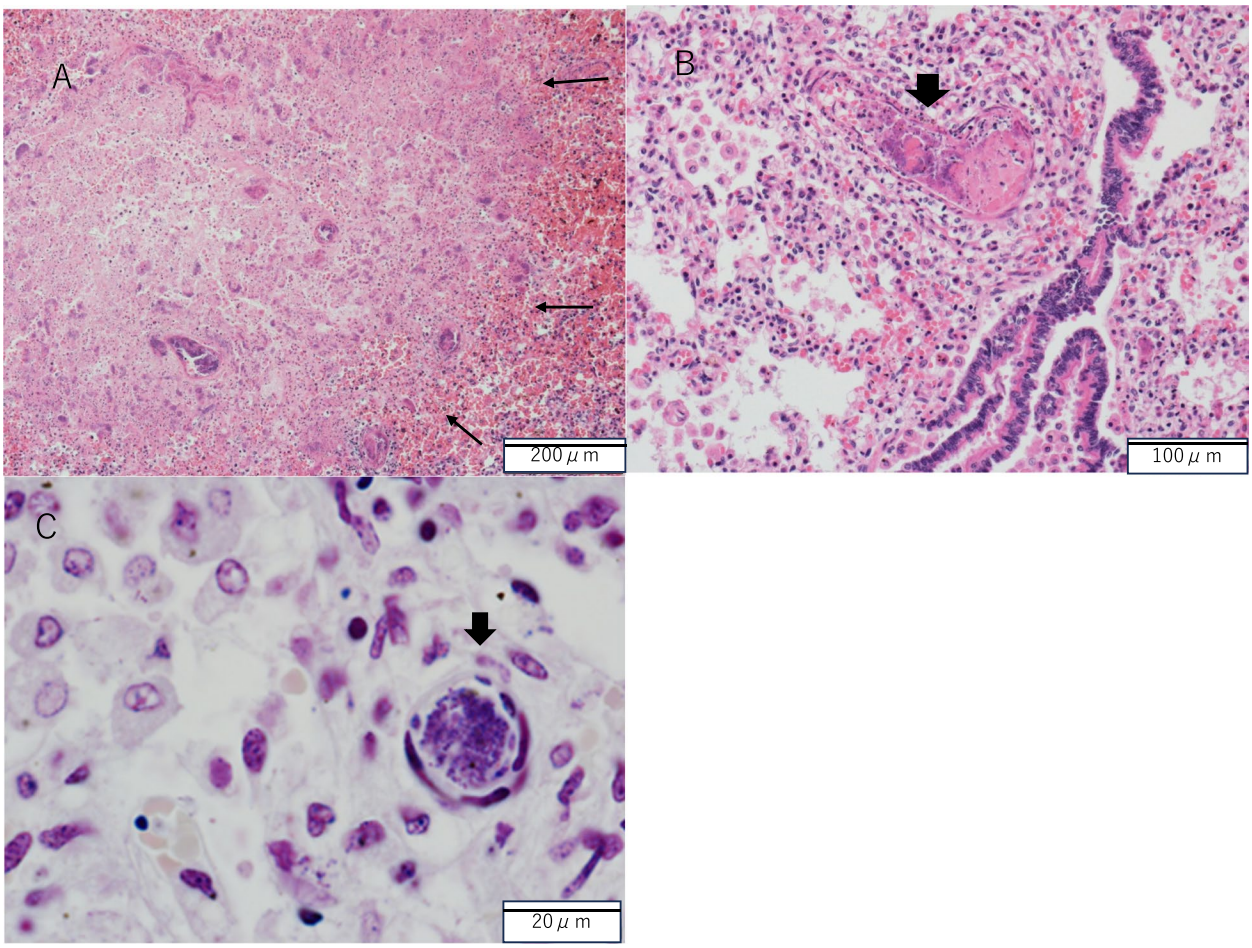

Fig. 2 Histopathology of the lung. **A** Localized necrotic nodules in the lung (black arrows). **B** Microthrombus containing a bacterial mass is seen in the blood vessels, indicating vasculitis (H&E stain, black arrows). **C** Gram positive cocci colonies in the blood vessels (black arrows)

all of which were negative. Perivascular inflammatory cell infiltrates were observed in the lungs, myocardium, kidneys, adrenal glands, brain, meninges, and liver. Micro-necrotic changes were observed in the kidneys and liver. Petechiae were observed in the occipital skin, myocardium, and pleura. Fibrin thromboemboli involved multiple renal glomeruli (Fig. 3). Hemophagocytosis was observed in the spleen, liver, bone marrow, and adrenal glands (Fig. 4). The liver sinusoids were dilated and highly congested.

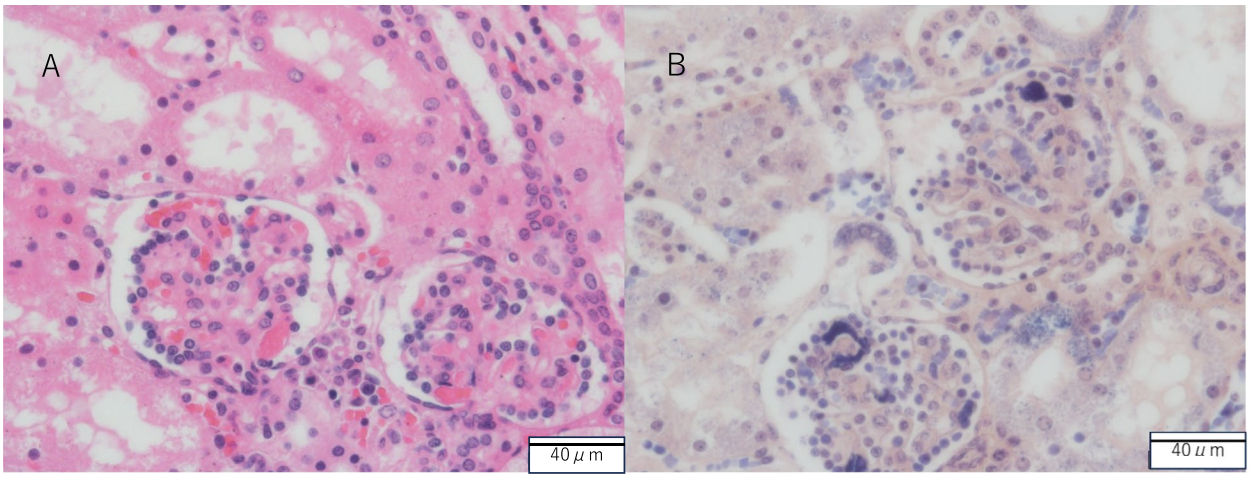

Fig. 3 Histopathology of the kidney. **A** Microemboli in the glomerular capillaries (H&E stain). **B** Microemboli in the glomerular capillaries (phosphotungstic acid, hematoxylin stain)

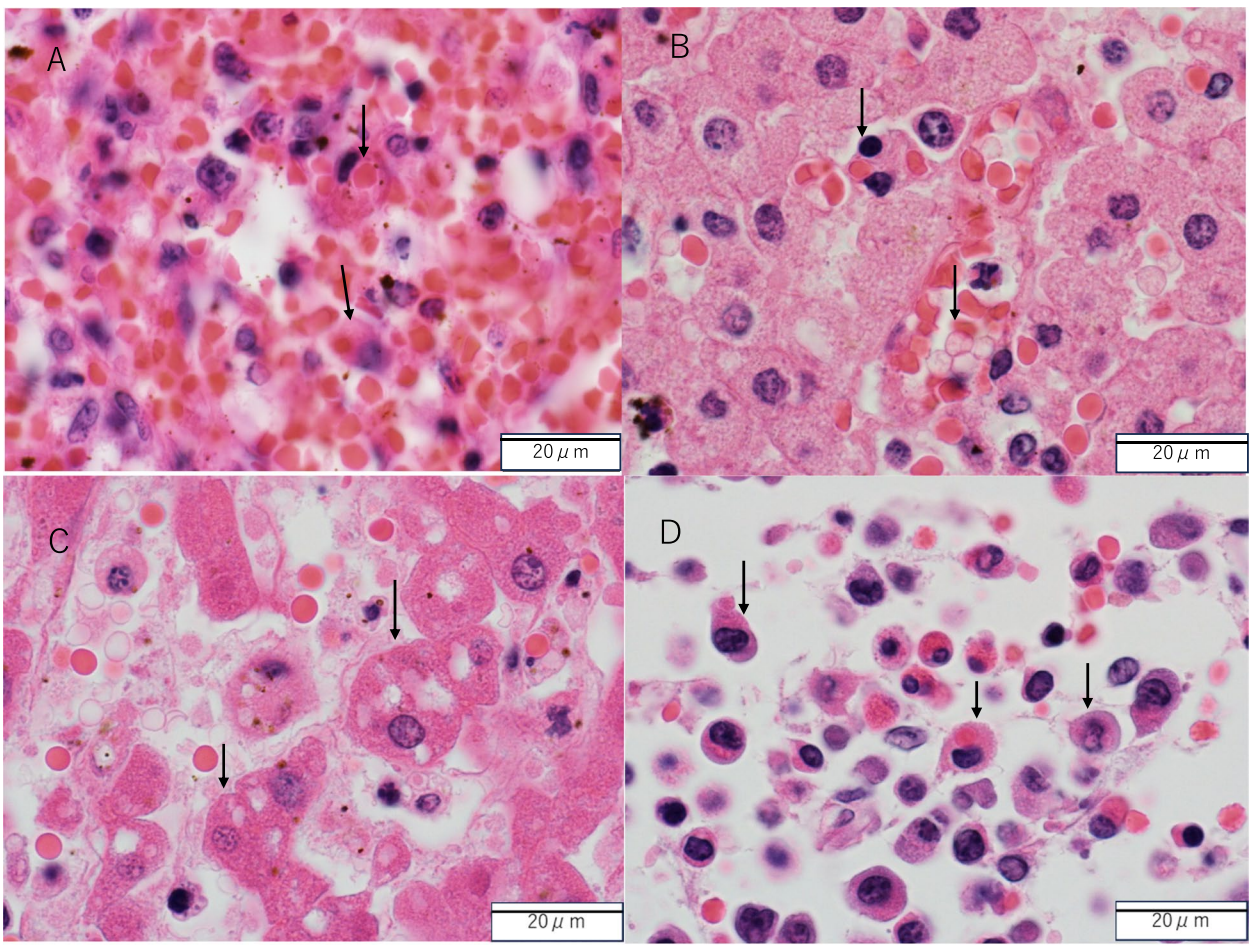

Fig. 4 Hemophagocytosis. **A** Spleen. **B** Adrenal gland. **C** Liver. **D** Bone marrow. Macrophages phagocytosing erythrocytes are visible (black arrows)

Immunohistochemical findings

Immunostaining results showed that the bacterial masses were positive for group A *Streptococcus* antibody (×1000; Abcam Corp., Cambridge MA, USA) (Fig. 5).

Post-mortem laboratory studies

Biochemical tests showed decreased plasma total protein of 32 g/L (normal value: 47–64 g/L), total bilirubin 88.9 μmol/L (normal value 2.8–54.4 μmol/L), direct bilirubin 65 μmol/L (normal range, 0.0–5.1 μmol/L), blood urea nitrogen 9 mmol/L (normal value 1.32–5.5 mmol/L), creatinine 36.2 μmol/L (normal value 10.6–23.8 μmol/L), and c-reactive protein 210.8 mg/L (normal value < 3.6 mg/L). Blood cultures were positive for *Streptococcus pyogenes* (group A Streptococcus). A drug toxicology screening test revealed trace amounts of caffeine in the blood, most likely from the mother's breast milk.

Discussion

A post-mortem diagnosis of fulminant group A streptococcal infection was made. Blood culture at autopsy was positive for *Streptococcus pyogenes* (type A Streptococcus). Coccal emboli were found in the lungs. Perivascular acute inflammatory cell infiltrates were found in the lungs, heart, kidneys, adrenal glands, arachnoid, and liver, leading to a diagnosis of sepsis. Microemboli were found in the glomerular vessels, suggesting that the patient was affected by disseminated intravascular coagulation (DIC). The diffuse hemorrhages in the adrenal cortices are consistent with Waterhouse–Friderichsen syndrome. Hemophagocytosis was found in multiple organs.

Fulminant hemolytic streptococcal infection is a condition of sudden onset and rapidly progressing septic shock caused by *Streptococcus pyogenes*, which exhibits beta-hemolysis. Although A *Streptococcus* causes fulminant infection more frequently, all streptococci that cause beta-hemolysis are potential causes (Stevens 1992).

Neonatal infections are commonly caused by group B *Streptococcus* and *E. coli*. Although Group A *Streptococcus* is a less frequent causative agent, the infection can be invasive and fatal (Germont et al. 2020). Neonatal group A *Streptococcus* (GAS) infection is rare. Miyairi et al. reported that, among 39 cases of neonatal invasive GAS disease, 24 cases of early onset neonatal invasive GAS disease were from mothers with puerperal sepsis. Early-onset neonatal GAS was thought to be caused mainly by transvaginal infection. Only 14 cases of late-onset GAS have been reported. Among those patients, 11 (78%) had non-specific signs, and 9 (64%) had fever only. The infection sources for late-onset GAS were soft tissue infection in 5 cases (33%), meningitis in 3 cases (20%), and fever in 2 cases (13%). Pneumonia was reported. Of the 11 mothers (73%) for whom information was available, 7 (47%) had no perinatal complication or pharyngitis (Miyairi et al. 2004).

In this case, no infection symptoms were reported in the mother postpartum. No infectious symptoms were observed in the patient at birth. In this case, a neutrophilic infiltrate was observed in the tonsils. Immunostaining with anti-type A *Streptococcus* antibody as the primary antibody showed positive results on the tonsil surface. This finding suggests spread from an upper respiratory tract infection.

Although it is a presumptive route of infection, this infant may have been infected with group A β-hemolytic *Streptococcus* by her brother, who had been treated for a streptococcal pharyngeal infection during her neonatal period.

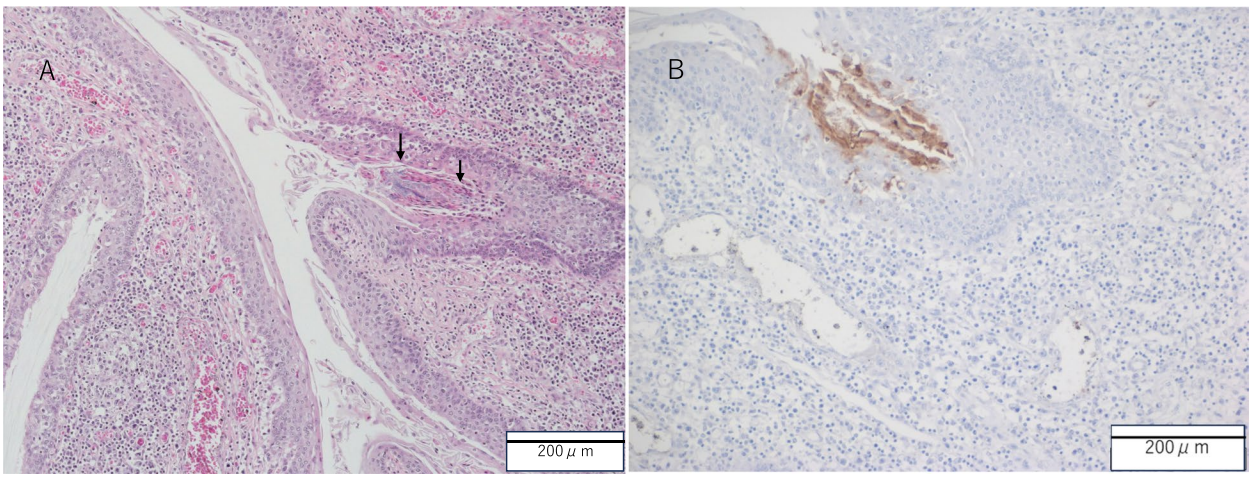

Fig. 5 Histopathology of the tonsil. **A** Mild neutrophilic infiltration of tonsils. A bacterial mass is visible in a superficial crypt (black arrows). **B** Immunostaining using anti-type A *Streptococcus* antibody as the primary antibody shows a mass of bacteria in a tonsillar crypt

Blood culture at autopsy was positive for *Streptococcus pyogenes* (group A *Streptococcus*). Coccal emboli were found in the lungs. Acute perivascular inflammatory cell infiltration was observed in the lungs, heart, kidneys, adrenal glands, arachnoid, and liver, leading to the diagnosis of sepsis. Thromboemboli were found in the glomerular vessels, suggesting that the patient was affected by DIC (Boral et al. 2016). At the emergency hospital, a blood test revealed anaemia with Hb 77 g/L. Histopathology revealed macrophages with erythrophagocytosis in the spleen, liver, adrenal glands, and bone marrow, which were thought to be the cause of the anaemia (Kazuhisa et al. 2006).

In this case, the patient had diffuse hemorrhage in both adrenal glands, suggesting concurrent Waterhouse–Friderichsen syndrome. Most cases are associated with *Neisseria meningitidis*, *Streptococcus pneumoniae*, or *Hemophilus influenzae* (Ventura et al. 2013; Emori et al. 2016; Chiwome 2022). Cases of Waterhouse–Friderichsen syndrome caused by *S. pneumoniae* almost always occur in patients with severe reticuloendothelial system dysfunction, especially hyposplenism or splenectomy. Only three earlier reports in the relevant literature have described Waterhouse–Friderichsen syndrome associated with GAS infection in an infant death (Gertner et al. 1992; Givner 1998; Karakousis et al. 2001). It was first described by Friderichsen in 1911 as a syndrome of characteristic skin rash with bilateral adrenal hemorrhage, abnormal coagulation, and cardiovascular failure (Friderichsen 1911). The syndrome progresses rapidly: it has an extremely poor prognosis. The fatality rate is 55–60%, with death occurring an average of 20.7 h after onset (Stephens et al. 2007).

In this case, there was low-grade fever without skin rash or other external surface findings typical of Waterhouse-Friderichsen syndrome. However, at autopsy, the diagnosis of Waterhouse-Friderichsen syndrome was made after bilateral adrenal hemorrhages, DIC, and bacteraemia were confirmed. Mild thymic atrophy was observed. This may be attributable to infection by GAS, which causes thymic changes early in the infection, including severe shrinkage of the organ, mainly because of the apoptosis-related depletion of immature CD4+CD8+thymocytes (Savino et al. 2007). The patient in this case had a slight fever of 37.5 °C. She rapidly went into shock, developing anuria and dyspnea following common cold-like symptoms that included lack of energy and decreased milk intake.

Parents of neonates must take great care with infection and isolate the child from siblings who have streptococcal infections. In this case, the sibling's streptococcal infection had already healed, and it was not possible to culture the bacteria and confirm that it was a similar type A *Streptococcus* strain.

Forensic pathologists have identified the following differential diagnosis in cases of newborn deaths where, as in the present case, the death occurred after nonspecific symptoms, such as persistent low-grade fever and lack of energy. In the case of unnatural deaths, the differential diagnosis includes shaken baby syndrome, poisoning, other types (masked) of blunt trauma, neglect, and hyperthermia of external causes; and in the case of natural causes, pneumonia, meningitis, gastroenteritis, myocarditis, and sepsis (Saukko and Knight 2016).

The forensic pathologist should carefully investigate the scene of death, the sleeping environment if the death occurred during sleep, and clarify at autopsy any trauma findings. To further clarify natural causes, bacterial culture of cardiac blood and spinal fluid, and viral culture of the intestinal contents should be performed.

Conclusions

This article reports a case of fulminant group A streptococcal infection discovered post-mortem. A forensic pathologist should suspect sepsis and perform an autopsy with blood cultures in cases of neonatal deaths involving low-grade fever.

Abbreviations

GAS	Group A *Streptococcus*
DIC	Disseminated intravascular coagulation
H&E	Hematoxylin and eosin stain

Acknowledgements

The authors thank Dr. Yutaka Tsutsumi, director of the Tsutsumi Pathology Clinic, for advice on immunostaining and pathology diagnosis.

Authors' contributions

FS performed the autopsy of this case and wrote the first draft of the manuscript. WI, CS, EO and MK performed pathology specimen preparation, biochemical tests, and drug screening tests. All authors have read and approved the final manuscript.

Funding

No funding was obtained for this study.

Availability of data and materials

Data sharing is not applicable to the study described herein because no dataset was generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Oral consent was received from the deceased's mother after informing her of the purpose of the case report. No identifying private details are described within the case report. Consequently, we did not need to receive written consent.

Competing interests

The authors declare that they have no competing interests.

Received: 5 June 2022 Accepted: 15 June 2023
Published online: 29 June 2023

References

Boral BM, Williams DJ, Boral LI (2016) Disseminated intravascular coagulation. Am J Clin Pathol 146:670–680
Carapetis JR, Steer AC, Mulholland EK, Weber K (2005) The global burden of group A streptococcal diseases. Lancet Infect Dis 5:685–694
Chiwome L (2022) A rare case of Waterhouse-Friderichsen syndrome without purpura secondary to haemophilus influenzae. Cureus 9:e9621
Emori K, Takeuchi N, Soneda J (2016) A case of Waterhouse-Friderichsen syndrome resulting from an invasive pneumococcal infection in a patient with a hypoplastic spleen. Case Rep Crit Care 2016:4708086
Friderichsen C (1911) A case of suprarenal apoplexy. Lancet 1:577–578
Germont Z, Bidet P, Plainvert C, Bonacorsi S, Bonacorsi S, Poyart C et al (2020) Invasive *Streptococcus pyogenes* infections in < 3-month-old infants in France: clinical and laboratory features. Front Pediatr 8:204
Gertner M, Rodriguez L, Barnett SH, Shah K (1992) Group A beta-hemolytic Streptococcus and Waterhouse-Friderichsen syndrome. Pediatr Infect Dis J 11:595–596
Givner LB (1998) Invasive disease due to group A beta hemolytic streptococci: continued occurrence in children in North Carolina. South Med J 91:333–337
Hua CZ, Yu H, Xu HM, Yang LH, Lin AW, Lyu Q et al (2019) A multi-center clinical investigation of invasive *Streptococcus pyogenes* infection in China, 2010–2017. BMC Pediatr 19:181
Karakousis PC, Page KR, Varello MA, Howlett PJ, Stieritz DD (2001) Waterhouse-Friderichsen syndrome after infection with Group A streptococcus. Mayo Clin Proc 76:1167–1170
Kato S, Yanazaki M, Hayashi K, Satoh F, Isobe I, Tsutsumi Y (2018) Fulminant group A streptococcal infection without gangrene in the extremities: analysis of five autopsy cases. Pathol Int 68:419–424
Kazuhisa K, Yamada S, Kinuwaki E, Naito M, Mitsuya H (2006) Peripheral hemophagocytosis: an early indicator of advanced systemic inflammatory response syndrome/ hemophagocytic syndrome. Shock 25:344–434
Martin WJ, Steer AC, Smeesters PR, Keeble J, Inouye M, Carapetis J et al (2015) Post infectious group A streptococcal autoimmune syndromes and the heart. Autoimmun Rev 14:710–725
Miyairi I, Berlingieri D, Protic J, Belko J (2004) Neonatal invasive group A streptococcal disease: case report and review of the literature. Pediatr Infect Dis J 23:161–165
Questionnaire Research Performed by the Japanese Society of Legal Medicine (2015) Weights and sizes of internal organs measured in forensic autopsy cases from 2009 to 2013 in Japan. Japanese society of legal medicine, research report. Available via DIALOG. http://www.jslm.jp/problem/zouki.pdf. Accessed 7 Oct 2022
Saukko P, Knight B (2016) Sudden death in infancy. In: Saukko P, Knight B (eds) Forensic pathology, 4th edn. CRC Press, London
Savino W, Dardenne M, Velloso LA, Silva-Barbosa SD (2007) The thymus is a common target in malnutrition and infection. Br J Nutr 98, Suppl. 1:S11–S16
Stephens DS, Greenwood B, Brandtzaeg P (2007) Epidemic meningitis, meningococcemia, and *Neisseria meningitides*. Lancet 369:2196–2210
Stevens DL (1992) Invasive group A streptococcus infections. Clin Infect Dis 14:2–13
Ventura F, Bonsignore A, Portunato F, Orcioni GF, Varnier OE, Stefano FD (2013) A fatal case of streptococcal and meningococcal meningitis in a 2-years-old child occurring as Waterhouse-Friderichsen Syndrome. J Forensic Leg Med 20:678–682
Weiss KA, Laverdière M (1997) Group A *Streptococcus* invasive infections: a review. Can J Surg 40:18–25

Publisher's Note